ASSESSMENT STRATEGIES FOR REDUCED RISK CIGARETTES

Comments by

Brown & Williamson Tobacco Corporation

Presented to

National Academy of Sciences Institute of Medicine

Committee to Assess the Science Base for Tobacco Harm Reduction

March 1, 2000

ASSESSMENT STRATEGIES FOR REDUCED RISK CIGARETTES

Brown & Williamson Tobacco Corporation

Macon, GA 31202-1056

March 1, 2000

PREFACE

In considering the issue of reduced risk cigarettes, one of the first questions one encounters is which strategy is the best way forward to have maximum positive impact on public health. A policy of encouraging abstinence from smoking is a clear path forward to achieving this objective. Perhaps not so clear is whether, in addition to encouraging abstinence from tobacco use, one should at the same time encourage "safer" smoking for those people who choose to smoke. It can be argued that the availability of reduced risk cigarettes may run counter to public health improvement as it may make smokers less inclined to quit or non-smokers more inclined to start. We know of no way to verify whether this would be the case or not. What we do know is that many people continue to smoke despite nearly universal awareness of the health risk of smoking (1). This leads to two questions:

1. What should be done for people who choose to smoke despite encouragement to abstain?
2. How can we justify depriving those people a lower risk option if such an option is feasible?

We believe that the most realistic and effective strategy is to encourage abstinence from tobacco use as the cornerstone of a policy of reducing smoking-related health risks. At the same time, for those people who choose to smoke, we believe there should be encouragement for cigarette companies to devote efforts toward the research and development of reduced risk products and allow consumers to be made aware of the potential benefits of such products so that they are at least free to choose among a range of options (1). We assume the existence of this committee and our participation in its deliberations is an indication of at least some degree of openness to consideration of the possibilities of making reduced risk products available to the public.

Another issue that the committee will encounter is the question of how to determine whether a particular cigarette modification will, in fact, result in a reduced risk for people who use the product. Based upon decades of responding to this issue, it is our view that the complexities of tobacco smoke, the mechanisms of human disease, and the measurement techniques available leave us in a situation where no test or measurement can predict, with scientific certainty, the impact on human health of a particular tobacco product or product characteristic. This is really not different, however, than the situation that the regulatory agencies face when they must make a determination about the acceptability of permitting public exposure to an environmental chemical, food additive, or new pharmaceutical. They must rely upon a collection of measures based upon epidemiology, toxicology, human clinical biomonitoring, and chemistry to make a judgement concerning acceptability. All of those assessment elements have their own particular uncertainties that ultimately make any judgement of acceptability fall short of

absolute scientific certainty. The primary difference between the situation with tobacco versus the situation with environmental chemicals, food additives, or pharmaceuticals is that, with the latter, there exists an established and agreed upon framework for making judgements about acceptability. That framework is the enabling legislation and subsequent regulations, and procedures the respective regulatory agencies have developed over the years. Within that framework, there are assessment measurements, success criteria, and other elements that, despite the uncertainties they each have, there are agreed upon procedures and criteria for their use and application toward a judgement of acceptability. Such a framework is lacking in the case of the assessment of potential reduction of risks associated with modified cigarettes.

We believe that developing and applying a framework for making assessments and judgements concerning potential benefits of modified cigarettes is a necessary element of any effort to assess the science base for tobacco harm reduction. Moreover, the successful application of such a framework must involve the cooperative efforts of members of the scientific, public health, regulatory, and tobacco products manufacturing communities. In order for such a framework to be successful, it must accommodate a known level of background risk as a starting point and seek to move modified products toward lower risk. We urge the committee to recognize the essential role of such a framework as a way forward in evaluating and judging the potential benefits of cigarettes modified to reduce smoking-related risks.

NOT ALL CIGARETTES POSE EQUAL RISKS

The remainder of this presentation will be primarily concerned with a discussion of the evidence that indicates that:

1. Reductions in cigarette smoke dose and smoke toxicity are likely to reduce smoking health-related risks.
2. Modifications of tobacco products can be made to achieve reductions in both smoke dose and smoke toxicity.
3. Responses of such modified products can be measured and quantified in a range of health-related tests judged to be appropriate.

The collective evidence supporting these conclusions comes from a combination of epidemiology, experimental toxicology, human clinical biomonitoring, and chemistry.

Since it is possible to measure and quantify the effects of modified cigarettes in various health-related measures, it should be possible to develop a mutually agreed framework for assessment of benefits of reduced risk cigarettes to arrive at a judgement with a reasonable degree of certainty of whether a particular modification is likely to move the product toward lower health risks.

SMOKE DOSE AND SMOKE TOXICITY LIKELY TO INFLUENCE SMOKING RISK

The collective literature related to smoking and health provides evidence that not all cigarettes or smoking practices result in equal health risks to smokers. As a general consideration, relative risks reported in epidemiological studies for several smoking-related diseases (e.g., lung cancer) vary over a relatively wide range with the most often cited risk of around 10 for lung cancer (2). Some of this variation is presumably due to differences in study methodologies and susceptibilities of the various populations studied. However, it is reasonable to ask whether a significant portion of this variation is due to differences between the study populations in the types and/or amounts of cigarettes smoked.

Several sources of evidence indicate that smoking-related risks are significantly influenced by smoke dose. Many studies have reported that smoking-related health risks are lower with fewer cigarettes smoked and shorter duration of smoking (2,3,4,5). It is believed that pipe and cigar smokers inhale less smoke than do cigarette smokers. This is believed to be the reason why risks for several smoking-related diseases are lower among pipe and cigar smokers than among cigarette smokers (6,7). Studies have reported that relative risks for lung cancer are lower in people who smoke filter cigarettes versus non-filter cigarettes (8,9,10,11,12,13). Likewise, there is some indication in the scientific literature that smokers of lower "tar" cigarettes may have lower risks for some smoking-related diseases than do smokers of higher "tar" cigarettes (13,14,15,16,17,18). For example, Hammond and co-workers reported a 20% reduction in risk for lung cancer in males and a 40%

reduction in the risk for female smokers of low tar cigarettes compared with smokers of high tar cigarettes (19). "Tar" yields of cigarettes as measured by the FTC method have declined approximately 50% from the 1950s to the present (20). An autopsy study reported that pathological changes in the bronchial epithelium of smokers were far less frequent among smokers who died in the 1970s compared with smokers who died in the 1950s (21). This finding prompted the authors of the study to predict a decline in the future in death rates from lung cancer among cigarette smokers. In fact, it has been reported that among males, there has been a decline in lung cancer rates since 1990 (22). This decline continues to the present. Finally, responses in experimental toxicity studies are almost invariably lower among low dose groups relative to higher dose groups (23,24,25). Collectively these observations indicate that product modifications that can be shown to result in lower smoke dose should move the product toward lower risk.

Investigators have suggested that smoking-related risks may be significantly influenced by smoke toxicity (26,27). Several studies have reported that people who smoke primarily black tobacco have higher risks for some smoking-related diseases than do people who smoke primarily blond tobacco (28,29,30,31,32). While the reasons for differences in risk are not known, hypotheses have been advanced that the difference may be due to higher levels of tobacco specific nitrosamines (TSNAs) in black tobacco (33). It has been suggested that use of charcoal filters may be a positive strategy toward lower risk cigarettes (34,35). This is presumably because of the ability of charcoal filters to reduce the levels of several vapor-phase constituents in smoke (36). Relative risks have been reported to be lower among users of moist snuff in Sweden (37,38,39,40) compared with

the United States (41). It has been suggested that this is due to the lower levels of TSNAs in Swedish moist snuff compared with U.S. moist snuff (38). Finally, responses in experimental toxicity studies [i.e., *in vitro* genetic toxicity (42,43,44,45,46), *in vitro* cytotoxicity (47,48), mouse skin painting (49), and inhalation studies (50,51)] have been shown to vary significantly per unit dose with different types of tobacco and other cigarette design parameters. Collectively these observations indicate that product modifications can be made which result in a smoke composition that produce lowered responses in such tests. As with modification of smoke dose, it may be feasible to modify the toxicity of smoke in a direction of reduced risk.

ASSESSMENT ELEMENTS

During this presentation, we will discuss several approaches for measuring health-related parameters of cigarette smoke. It is important to recognize that cigarette smoke is actually composed of two distinct phases, a vapor phase, and a particulate phase (52). A number of smoke constituents have been identified which are believed to play a role in smoking-related diseases. Some of these constituents exist only in the vapor phase, some exist only in the particulate phase, and some may equilibrate between the two phases depending upon their physical and chemical properties and the environmental conditions in which they exist. We mention this only to bring to your attention that some strategies for lower risk cigarettes may focus on one phase of smoke as opposed to whole smoke. Also, because of the logistics of collecting smoke samples, some methods of smoke assessment may measure only one of these phases, which is typically the particulate phase or "tar".

Another concept that is important to appreciate is the concept of modifying the ***quantity*** of smoke a person gets in contrast to the ***quality*** of smoke a person gets. Modification of the quantity of smoke addresses the issue of total smoke dose. It is possible to modify smoke dose without modifying the relative proportions of individual constituents within the smoke. An example of this would be to reduce the density of tobacco in the cigarette. On the other hand, modification of the quality of smoke addresses the issue of modifying the proportions of constituents within the smoke and thereby the relative toxicity of the smoke. Examples of this might include use of activated charcoal in a filter to selectively reduce

some vapor-phase smoke constituents or use of alternative tobacco curing techniques to reduce the levels of TSNAs in smoke.

Epidemiology

Human epidemiology is among the assessment elements potentially available that can be applied to an assessment of whether modified cigarettes are, in fact, lower risk cigarettes. It has been instrumental in pointing to the associations of tobacco use and increased risks of various diseases in humans. As indicated above, it has also pointed to possible differences in risk resulting from use of:

- Pipe and cigar versus cigarettes (6,7)
- Black versus blond tobacco (28,29,30,31,32)
- Filter versus non-filter cigarettes (8,9,10,11,12,13)
- High tar versus low tar, cigarettes (13,14,15,16,17,18,19)
- Charcoal versus non-charcoal filters (53)
- Swedish moist snuff versus American moist snuff (38)

Unfortunately epidemiology cannot tell us the mechanism(s) of how smoking might contribute to disease and what modifications need to be made in cigarettes to reduce those risks. Its greatest strength is that it provides information about the product as actually used by the species of interest, namely, humans. It eliminates uncertainties resulting from use

of surrogates for fresh whole smoke, human smoking behavior, and human health effects endpoints. It evaluates effects of both smoke quality and quantity.

Its weaknesses are that it is subject to confounding from uncontrolled variables within study populations (54). . This shortcoming becomes increasingly critical as observed associations become weaker as may be the case when making comparisons of conventional cigarettes with modified cigarettes. It is subject to bias resulting from selection of study design and methodology parameters. As with confounding, this shortcoming becomes increasingly critical, as observed associations become weaker as may be the case with assessment of different types of cigarettes. The ability of an epidemiological study to detect a small effect is related to the size of the study. However, even a small effect in a large population is difficult to detect even though it may be significant from a public health point of view. Perhaps the biggest shortcoming of the use of epidemiology to assess modified cigarettes is the length of time it would take to get meaningful results. For assessment of a new modified cigarette, a retrospective study design would not be feasible. A prospective study would require approximately 7-15 years to complete. Moreover, it would require a large number of people to have smoked a novel product to conduct an epidemiological study. Perhaps their most promising use would be for long-term surveillance of people using a modified product in the years following its market introduction.

Human Biomonitoring

Human biomonitoring for presence of cigarette smoke constituents in body fluid samples is another valuable approach for assessment of modified cigarettes (55). A number of cigarette smoke constituents have been evaluated in this manner. The most common is measurement of nicotine and its metabolites in blood, saliva, and urine (56,57). In addition, adducts derived from smoke constituents including nitrosamines, polycyclic aromatic hydrocarbons (PAHs), and aromatic amines have been measured in various body fluids and tissue samples (58,59,60).

In addition to measures of smoke constituents in body fluids and tissues, a number of functional end points have been examined for measures of cigarette smoke exposure. These include:

- Platelet aggregation (61)
- Various serum lipids (62)
- Pulmonary function measures (63)
- Arterial wall thickness (64,65)
- Urine mutagenicity (66,67)
- Mutation spectra of selected genes (68)

An obvious strength of human biomonitoring is that it can provide an indication of cigarette smoke exposures in humans under conditions of actual cigarette use, thus taking

into account human smoking behavior. This minimizes uncertainties of use of surrogates or indirect measures of exposure. The techniques are generally not prohibitively expensive or time consuming. Samples and measurement techniques are generally available.

For most biomarkers, the majority of research investigations have focused on being able to distinguish between smokers versus non-smokers, or people who have been exposed to ETS versus not exposed to ETS. They typically have not focused on discrimination of people who smoke different amounts or types of cigarettes. As a consequence, the majority of the techniques reported have not been validated as a means of discriminating differences between people who smoke different amounts or types of cigarette products. Most end points (both chemical and functional) are not specific to tobacco (69). Therefore, significant background responses are often observed in non-smokers. Moreover, responses can be highly variable among test subjects. It is not uncommon for such techniques to be unable to discriminate even between smokers and non-smokers (69,70,71). In contrast to standardized chemical and toxicological tests conducted in accordance with GLP regulations typical for regulatory submissions, the methods used for most biomonitoring studies are not standardized or cross checked between laboratories (72). This makes it difficult to make comparisons between laboratories and investigators. There is also the issue of uncertainty of the role of a given endpoint in smoking associated disease and what a reduction in response in a particular test might mean as far as smoking-related disease is concerned.

Despite these uncertainties several techniques have been explored. It might be assumed that if a technique is able to detect exposure to ETS, it might have promise for detecting significant differences in exposures comparing people who smoke conventional versus modified cigarettes. This assumption would require validation. Nevertheless, a number of measures have been reported that either detect differences in people who smoke different amounts of tobacco, different types of tobacco, or between people who are self reported to be exposed to ETS versus people not exposed to ETS. These measures include:

-Nicotine and its metabolites in urine, serum, saliva (56,73)

- Expired CO, COHb (55,74,75)

- TSNA urinary metabolites (e.g., NNAL) (76,77)

- 4-Aminobiphenyl hemoglobin adducts (78,79,80,81,82)

- Acrylamide hemoglobin adducts (83)

- Acrylonitrile adducts with hemoglobin (83,84)

- Benzene (exhalate or levels of metabolites in body fluids) (85,86,87)

- PAH adducts (60,76,88,89)

- Platelet aggregation (90)

- Fibrinogen in plasma (91)

- Carotid wall thickness (64,65)

- Some serum lipids (e.g., total cholesterol, HDL) (92,93)

- Urine mutagenicity (66,67)

Experimental Toxicology

A wide range of experimental toxicity tests has been explored in attempts to characterize health-related effects of various cigarette types and design parameters. The three largest categories of the types of tests employed are:

1. Inhalation tests of fresh whole smoke conducted primarily in rodents (23,24,50,51,94).
2. Skin painting tests of whole smoke or particulate phase condensate conducted primarily in mice (25,95).
3. Short term *in vitro* tests of smoke particulate phase condensate or whole smoke for genetic and cytotoxicity conducted in a variety of biological systems (42,43,44,46,48,96), of which, the Ames *salmonella* mutagenicity assay (97) is by far the most frequently reported.

The primary advantage of experimental toxicology is the ability to isolate and focus on test elements of interest by controlling confounding environmental factors. The test methods are readily available, relatively short-term, and of a reasonable cost. The methodologies are well standardized and can be conducted in accordance with GLP regulations. Furthermore, there is an abundant background literature for comparisons.

Experimental toxicology has a number of uncertainties. Researchers have noted that most of the classical toxicity tests conducted in laboratory animals have failed to consistently reproduce the human diseases associated with cigarette smoking (98,99,100). Therefore,

the commonly used test species may not be good models for how humans respond to smoking. For some testing methodologies, only smoke condensate (particulate matter) is tested as a surrogate for fresh whole smoke. There may also be uncertainty about the relevance of the test end point. For example, we do not know the relevance of mouse skin tumors to human lung cancer. For that reason, we do not know with certainty what a reduction in potency in such a test of smoke condensate from a modified cigarette means for human health risks. Finally it is not uncommon to observe what appears to be conflicting responses in various tests. For example, smoke from cigarettes composed of only burley tobacco is more potent than smoke from flue-cured tobacco in the Ames test but less potent in the mouse skin painting test (42).

Nevertheless, toxicology tests have demonstrated the ability to distinguish differences in different product types and cigarette design parameters including differences in:

- Types of tobacco (42,43,46,48,49,50,101)
- Filter ventilation (46,49)
- Charcoal versus non-charcoal filters (47)
- Tobacco substitutes (50,51)
- Smoke particulate versus vapor phase (102)
- Novel cigarette products (103,104)
- Removal of tobacco protein (105)
- Other cigarette design variables (49,106)

Smoke Chemistry

More than 4000 compounds have been identified in cigarette smoke through the use of analytical chemistry (107). Some of these compounds are believed to play an important role in the health risks associated with cigarette smoking (108,109,110). Examples include:

- Tobacco specific nitrosamines (111)
- Volatile nitrosamines (112)
- Polycyclic aromatic hydrocarbons (113,114)
- Various aldehydes (115,116)
- "Tar", nicotine and carbon monoxide (110,117)
- Various aromatic amines (118)
- Nitrogen oxides (119,120)
- Hydrogen cyanide (121)
- Ammonia (122)
- Catechol, hydroquinone, and various other phenols (123,124)
- Benzene, toluene, xylene (115,125)
- Pyridine and quinoline (118)
- Isoprene and butadiene (125)
- Various heavy metals (126,127,128)
- Free radicals (119,129,130)
- Others (131,132)

Smoke chemistry allows the ability to focus on particular smoke constituents of concern. Very low levels of constituents in smoke and very small differences of individual smoke constituents in different products can be detected. The overall simplicity versus complexity of cigarette smoke as it might be influenced by cigarette modifications can be assessed. Measurement techniques for smoke constituents are readily available and can be obtained relatively quickly, and at a reasonable cost. There is an abundant background literature for comparisons of levels of smoke constituents in various products.

The primary weakness of smoke chemistry is that it is not a biological endpoint. Focusing on a particular constituent requires an examination of the relevance of the constituent and reduction of the levels of the constituent to smoking associated disease in humans. The analytical determination requires the collection of a sample of smoke under some defined set of machine smoking parameters. Many aspects of the collection parameters can significantly influence the levels of various constituents measured. Therefore the levels of constituents measures in smoke can be highly dependent upon the smoke collection methodology.

Despite these limitations the use of smoke chemistry has been shown to distinguish differences in different product types including differences in chemistry resulting from:

- Different types of tobacco/blends (49,133, 134,135,136)
- Filtration and filter ventilation (49,137,138)

- Charcoal versus non-charcoal filters (116)

- Tobacco substitutes (139,140,141)

- Novel cigarette products (142,143)

- Other cigarette design variables (132,144,145,146)

DISCUSSION AND RECOMMENDATIONS

The collective smoking and health research literature provides evidence that not all cigarettes or smoking practices pose equal risks. This indicates that it is possible to develop products that pose lower risks than others do. There is also evidence that both smoke dose and smoke toxicity may play roles in influencing tobacco smoke risk. Moreover, the effects of different tobacco products can be detected and quantified in a variety of health related measures. These measures include epidemiology, biomonitoring, experimental toxicology, and analytical chemistry. However, the complexities of tobacco smoke, mechanisms of human disease, and the measurement techniques available leave us in a situation where no test or measurement can predict, with scientific certainty, the impact on human health of a particular tobacco product or product characteristic. Nevertheless, because various measurement techniques have demonstrated an ability to discriminate differences in health-related responses to different tobacco product types, it should be possible to construct a measurement and assessment framework that can be applied to cigarettes modified to reduce risks. In order for such a framework to be successful, it would require the assistance and cooperation of members of the scientific, public health, regulatory, and tobacco products manufacturing communities.

Because of the uncertainties of any given health-related measure, an assessment approach should draw upon a wide range of assessment elements including smoke chemistry, experimental toxicology, human smoking behavior, human biomonitoring, and long-term human surveillance.

Perhaps the most important challenge to evaluating the benefits of reduced risk cigarettes is the evaluation of the acceptance of such products by the public. There are very few strategies of which we are aware for reducing smoke dose and/or smoke toxicity that can be achieved without some degree of alteration of the taste and/or other performance characteristics of the product. This frequently results in the consumer simply not liking the product compared to conventional products and being unwilling to use it. As might be expected, the greater the degree of novelty of the modification used to achieve reduced risks, the greater the likelihood that the consumer will dislike the product. Obviously, if a product is not accepted, it will provide no benefit to anyone despite its technical innovations.

Therefore, if one believes that development and introduction of reduced risk cigarettes is a positive strategy toward risk reduction among smokers, then the issue of how gradually versus rapidly technological innovations should be introduced into cigarettes in the market place deserves consideration. A product with very novel technological innovations is likely to offer relatively more health-related improvements than a product with more modest modifications. However, such a product is more likely to be rejected by consumers. If this were the case, potential benefits would never by realized. On the other

hand, a product modification strategy that gradually incorporates modest innovations in a step-by-step process whereby each change is not so great as to result in consumer rejection may, in the end, result in the greatest reductions in health risks as it is more likely to be used by consumers. At this point, it is not possible to know where the balance of product novelty, potential benefits, and consumer acceptance may be struck. Therefore, we believe that, because both approaches have the potential to reduce health risks for people who chose to smoke, both revolutionary/novel and gradual, continuous, step-by-step approaches should be pursued. In order to encourage both approaches we feel that product assessment approaches should take into account the nature of the modification employed (i.e., novel versus modest step-by-step) by tailoring the scope of assessment elements and success criteria according to the extent and novelty of the modification.

Another consideration that is critical to achieving the maximum benefit from reduced risk cigarettes is that of consumer awareness about improved products. Very few people would be willing to select what they perceive as an inferior-performing product in the absence of some other benefit they want. For example, fewer people would be willing to use diet soft drinks if they were not aware that they are reduced in calorie content. The same is the case with reduced risk cigarettes. We believe it is inevitable that technological innovations that can bring about significant health-related improvements in cigarettes will also result in alterations in the performance of the product, which will be perceivable by consumers. If the consumer is made aware of the potential benefits of the modified product, they may be willing to accept a reduction in performance. We, therefore, believe that it is vital to permit accurate communication to consumers about potential benefits resulting from

reduced risk cigarettes. If the collective judgement of appropriate scientists (based on a mutually agreed upon assessment framework) is that a particular product modification has moved the product toward lower health risks, from a public health point of view, people who choose to smoke should be made aware of such a product thus allowing them the opportunity to make an informed choice. A mutually agreed framework for communication to the public about reduced risk cigarettes is needed. The nature of communications to consumers about product attributes should be tailored according to the extent and novelty of the modification and potential benefits it may offer.

BIBLIOGRAPHY AND REFERENCES

1 Viscusi, W. K. "Constructive Cigarette Regulation," *Duke Law Journal*, 47:6 (April 1998), pp. 1095-1131.

2 US Department of Health, Education, and Welfare, Public Health Service. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*, Public Health Service Publication No, 1103, US Government Printing Office, 1964, pp. 161-165.

3 Doll, R. and Peto, R. "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," *British Medical Journal*, 2 (December 1976), pp. 1525-1536.

4 US Department of Health, Education, and Welfare, Public Health Service, Office of Smoking and Health. *Smoking and Health: A Report of the Surgeon General*, DHEW Publication No. (PHS) 79-50066, US Government Printing Office, 1979, Chapter 5.

5 Doll, R., Peto, R., Wheatley, K., Gray, R. and Sutherland, I. "Mortality in Relation to Smoking: 40 Years' Observations on Male British Doctors," *British Medical Journal*, 309 (October 1994), pp. 901-911.

6 US Department of Health, Education, and Welfare, Public Health Service, Office of Smoking and Health. *Smoking and Health: A Report of the Surgeon General*, DHEW Publication No. (PHS) 79-50066, US Government Printing Office, 1979, Chapter 13.

7 International Agency for Research on Cancer. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 38, Tobacco Smoking*, IARC, 1986, pp. 199-221.

8 Bross, I. D. J. and Gibson, R. "Risk of Lung Cancer in Smokers Who Switch to Filter Cigarettes," *American Journal of Public Health and Nations Health*, 58:8 (August 1968), pp. 1396-1403.

9 Dean, G., Lee, P. N., Todd, G. F., and Wicken, A. J. "Report on a Second Retrospective Mortality Study in North-East England - Part I. Factors Related to Mortality from Lung Cancer, Bronchitis, Heart Disease and Stroke in Cleveland County, with Particular Emphasis on the Relative Risk Associated with Smoking Filter and Plain Cigarettes," Tobacco Research Council, London, 1977, Research Paper No. 14.

10 Lubin, J. H. "Modifying Risk of Developing Lung Cancer by Changing Habits of Cigarette Smoking," *British Medical Journal*, 289 (October 1984), p. 921.

11 Wynder, E. L. and Kabat, G. C. "The Effect of Low-Yield Cigarette Smoking on Lung Cancer Risk," *Cancer*, 62:6 (September 1988), pp. 1223-1230.

12 Lubin, J. H., Blot, W. J., Berrino, F., Flamant, R., Gillis, C. R., Kunze, M., Schmahl, D., and Visco, G. "Patterns of Lung Cancer Risk According to Type of Cigarette Smoked," *International Journal of Cancer*, 33:5 (May 1984), pp. 569-576.

13 Benhamou, S, Benhamou, E., Auquier, A., and Flamant, R. "Differential Effects of "Tar" Content, Type of Tobacco, and Use of a Filter on Lung Cancer Risk in Male Cigarette Smokers," *International Journal of Epidemiology*, 23:3 (June 1994), pp. 437-443.

14 Garfinkel, L. and Stellman, S. D. "Smoking and Lung Cancer in Women: Findings in a Prospective Study," *Cancer Research*, 48:23 (December 1988), pp. 6951-6955.

15 Sauer, W. H., Berlin, J. A., Miles, Carolyn G., Strom. Brian L., Kimmel, S. E. "Cigarette Yield and the Risk of Myocardial Infraction in Smokers," 72nd Scientific Sessions of *Circulation*, Atlanta, GA, November 7-10, 1999, Paper 2756.

16 Kaufman, D. W., Palmer, J. R., Rosenberg, L., Stolley, P., Warshauer, E., and Shapiro, S. "Tar Content of Cigarettes in Relation to Lung Cancer," *American Journal of Epidemiology*, 129:4 (April 1989), pp. 703-711.

17 Vuctuc, C. and Kunze, M. "Lung Cancer Risk in Women in Relation to Tar Yields of Cigarettes," *Preventive Medicine*, 11:6 (November 1982), pp. 713-716.

18 Tang, J-L, Morris, J. K., Wald, N. J., Hole, D., Shipley, M., and Tunstall-Pedoe, H. "Mortality in Relation to "Tar" Yield of Cigarettes, *British Medical Journal*, 311 (December 1995), pp. 1530-1533.

19 Hammond, E. C., Garfinkel, L., Seidman, H., and Lew, E. A. "Some Recent Findings Concerning Cigarette Smoking," in Hiatt, H. H., Watson, J. D., and Winstein, J. A., Eds., *Origins of Human Cancer. Book A: Incidence of Cancer in Humans*, Cold Spring Harbor Laboratory, 1977, pp. 101-112.

20 Hoffmann, D., Djordjevic, M. V., and Hoffmann, I. "The Changing Cigarette," *Preventive Medicine*, 26:4 (July-August 1997), pp. 427-434.

21 Auerbach, O., Hammond, E. C., and Garfinkel, L. "Changes in Bronchial Epithelium in Relation to Smoking, 1955-1960 vs. 1970-1977," *The New England Journal of Medicine*, 300:8 (February 1979), pp. 381-386.

22 Wingo, P. A., Ries, L. A. G., Giovino, G. A., Miller, D. S., Rosenberg, H. M., Shopland, D. R., Thun, M. J., and Edwards, B. K. "Annual Report to the Nation on the Status of Cancer, 1973-1996, With a Special Section on Lung Cancer and Tobacco Smoking," *Journal of the National Cancer Institute*, 91:8 (April 1999), pp. 675-690.

23 Gaworski, C. L., Dozier, M. M., Heck, J. D., Gerhart, J. M., Rajendran, N., David, R. M., Brennecke, L. H., and Morrissey, R. "Toxicologic Evaluation of Flavor Ingredients Added to Cigarette Tobacco: 13-Week Inhalation Exposure in Rats," *Inhalation Toxicology*, 10:4 (1998), pp. 357-381.

24 Gaworski, C. L., Dozier, M. M., Gerhart, J. M., Rajendran, N., David, R. M., Brennecke, L. H., Aranyi, C., and Heck, J. D. "13-Week Inhalation Toxicity Study of Menthol Cigarette Smoke," *Food and Chemical Toxicology*, 35:7 (July 1997), pp. 683-692.

25 Gaworski, C. L., Heck, J. D., Bennett, M. B., and Wenk, M. L. "Toxicologic Evaluation of Flavor Ingredients Added to Cigarette Tobacco: Skin Painting Bioassay of Cigarette Smoke Condensate in SENCAR Mice," *Toxicology*, 139:1-2 (November 1999), pp. 1-17.

26 Wynder, E. L. and Muscat, J. E. "The Changing Epidemiology of Smoking and Lung Cancer Histology," *Environmental Health Perspectives*, 103, Supplement 8 (November 1995), pp. 143-148.

27 Stellman, S. D., Muscat, J. E., Hoffmann, D., and Wynder, E. L. "Impact of Filter Cigarette Smoking on Lung Cancer Histology," *Preventive Medicine*, 26 (1997), pp. 451-456.

28 Joly, O. G., Lubin, J. H., and Caraballoso, M. "Dark Tobacco and Lung Cancer in Cuba," *Journal of the National Cancer Institute*, 70:6 (June 1983), pp. 1033-1039.

29 Benhamou, S., Benhamou, E., Tirmarche, M., Flamant, R. "Lung Cancer and Use of Cigarettes: A French Case-Control Study," *Journal of the National Cancer Institute*, 74:6 (June 1985), pp. 1169-1175.

30 Bosch, F. X., and Cardis, E. "Black Tobacco and Cancer: Introducing an Epidemiological Review," *European Journal of Cancer*, 27:11 (1991), pp. 1345-1348.

31 Benhamou, E. and Benhamou, S. "Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk VI: Lung Cancer," *European Journal of Cancer*, 29A:12 (1993), pp. 1778-1780.

32 Armadans-Gil, L., Vaqué-Rafart, J., Rosselló, J., Olona, M., and Alsedà, M. "Cigarette Smoking and Male Lung Cancer Risk with Special Regard to Type of Tobacco," *International Journal of Epidemiology*, 28:4 (August 1999), pp. 614-619.

33 Fischer, S., Spiegelhalder, B., and Preussmann, R. Tobacco-specific Nitrosamines in European and USA Cigarettes," *Archiv für Geschwulsforschung*, 60:3 (1990), pp. 169-177.

34 Slade, J. and Henningfield, J. E. "Tobacco Product Regulation: Context and Issues," *Food and Drug Law Journal*, 53 Supplement (1998), pp. 43-74.

35 Djordjevic, M. V., Hoffmann, D., Thompson, S., and Stellman, S. D. "Tobacco and Mainstream Smoke Chemistry of the Leading U.S. and Japanese Cigarettes," 52nd Tobacco Science Research Conference, Atlanta, GA, September 13-16, 1998, Paper #59.

36 Williamson, J. T., Graham, J. F., and Allman, D. R. "The Modification of Cigarette Smoke by Filter Tips," *Beiträge zur Tabakforschung*, 3 (August 1965), pp. 233-242.

37 Bolinder, G. "Overview of Knowledge of Health Effects of Smokeless Tobacco. Increased Risk of Cardiovascular Diseases and Mortality Because of Snuff," *Lakartidningen*, 94:42 (October 1997), pp. 3725-3731.

38 Nilsson, R. "A Qualitative and Quantitative Risk Assessment of Snuff Dipping," *Regulatory Toxicology and Pharmacology*, 28:1 (August 1998), pp. 1-16.

39 Lewin, F., Norell, S. E., Johansson, H., Gustavsson, P., Wennerberg, J, Biörklund, A., and Rutqvist, L. E. "Smoking Tobacco, Oral Snuff, and Alcohol in the Etiology of Squamous Cell Carcinoma of the Head and Neck. A Population-Based Case-Referent Study in Sweden," *Cancer*, 82:7 (April 1998), pp. 1367-1375.

40 Schildt, E.B., Eriksson, M., Hardell, L, and Magnuson, A. "Oral Snuff, Smoking Habits and Alcohol Consumption in Relation to Oral cancer in a Swedish Case-Control Study," *International Journal of Cancer*, 77:3 (July 1998), pp. 341-346.

41 US Department of Health, and Human Services, Public Health Service. *The Health Consequences of Using Smokeless Tobacco-A Report of the Advisory Committee to the Surgeon General*, NIH Publication No. 86-2874, US Government Printing Office, 1986, Chapter 2.

42 Mizusaki, S., Takashima, T., and Tomaru, K. "Factors Affecting Mutagenic Activity of Cigarette Smoke Condensate in *Salmonella Typhimurium* TA 1538," *Mutation Research*, 48:1 (1977), pp. 29-36.

43 Mizusaki, S., Okamoto, H., Akiyama, A., and Fukuhara, Y. "Relation Between Chemical Constituents of Tobacco and Mutagenic Activity of Cigarette Smoke Condensate," *Mutation Research*, 48:3-4 (July 1977), pp. 319-326.

44 DeMarini, D. M. "Genotoxicity of Tobacco Smoke and Tobacco Smoke Condensate," *Mutation Research*, 114:1 (January 1983), pp. 59-89.

45 Brunnemann, K. D., Hoffmann, D., Gairola, C. G., and Lee, B. C. "Low Ignition Propensity Cigarettes: Smoke Analysis for Carcinogens and Testing for Mutagenic Activity of Smoke Particulate Matter," *Food Chemical Toxicology*, 32:10 (October 1994), pp. 917-922.

46 Tewes, F. J., Meisgen, T. J., Gomm, W. A., Roemer, E., and Carchman, R. A. "Cigarette Parameters That Influence the Mutagenicity of Mainstream Smoke Condensate," *The Toxicologist*, 48 (1-S) (March 1999), p. 125.

47 Bombick, D. W., Bombick, B. R., Ayres, P. H., Putnam, K., Avalos, J, Borgerding, M. F., and Doolittle, D. J. "Evaluation of the Genotoxic and Cytotoxic Potential of Mainstream Whole Smoke and Smoke Condensate from a Cigarette Containing a Novel Carbon Filter," *Fundamental and Applied Toxicology*, 39:1 (September 1997), pp. 11-17.

48 Bombick, D. W., Putnam, K., and Doolittle, D. J. "Comparative Cytotoxicity Studies of Smoke Condensate from Different Types of Cigarettes and Tobaccos," *Toxicology in Vitro*, 12 (1998), pp. 241-249.

49 Gori, G. B., Ed. *Report No. 3. Toward Less Hazardous Cigarettes. The Third Set of Experimental Cigarettes*, DHEW Publication No. (NIH) 77-1280, US Government Printing Office, 1977.

50 Dontenwill, W., Chevalier, H-J., Harke, H-P., Lafrenz, U., Reckzeh, G., and Schneider, B. "Investigations on the Effects of Chronic Cigarette-Smoke Inhalation in Syrian Golden Hamsters," *Journal of the National Cancer Institute*, 51:6 (December 1973), pp. 1781-1807.

51 Bernfeld, P., Homburger, F., Soto, E., and Pai, K. J. "Cigarette Smoke Inhalation Studies in Inbred Syrian Golden Hamsters," *Journal of the National Cancer Institute*, 63:3 (September 1979), pp. 675-689.

52 Norman, V. "An Overview of the Vapor Phase, Semivolatile and Nonvolatile Components of Cigarette Smoke," *Recent Advances in Tobacco Science*, 3 (1977), pp. 28-58.

53 Wynder, E. L. and Hoffmann, D. "Smoking and Lung Cancer: Scientific Challenges and Opportunities," *Cancer Research*, 54:20 (October 1994), pp. 5284-5295.

54 Taubes, G. "Epidemiology Faces Its Limits," *Science*, 269 (July 14, 1995), pp. 164-169.

55 Henderson, R. F., Bechtold, W. E., Bond, J. A., and Sun, J. D. "The use of Biological Markers in Toxicology," *Critical Reviews in Toxicology*, 20:2 (1989), pp. 65-82.

56 Scherer, G. "Smoking Behaviour and Compensation: A Review of the Literature," *Psychopharmacology*, 145:1 (July 1999), pp. 1-20.

57 Benowitz, N. L. "Cotinine as a Biomarker of Environmental Tobacco Exposure," *Epidemiologic Reviews*, 18:2 (1996), pp. 188-204.

58 Scherer, G. and Richter, E. "Biomonitoring Exposure to Environmental Tobacco Smoke (ETS): A Critical Reappraisal," *Human & Experimental Toxicology*, 16 (1997), pp. 449-459.

59 Perera, F., Mayer, J., Santella, R. M., Brenner, D., Jeffrey, A., Latriano, L., Smith, S., Warburton, D., Young, T. L., Tsai, W. Y., Hemminki, K, and Brandt-Rauf, P. "Biologic Markers in Risk Assessment for Environmental Carcinogens," *Environmental Health Perspectives*, 90 (1991), pp. 247-254.

60 Tang, D., Warburton, D., Tannenbaum, S. R., Skipper, P., Santella, R. M., Cereijido, G. S., Crawford, F. G., and Perera, F. P. "Molecular and Genetic Damage from Environmental Tobacco Smoke in Young Children," *Cancer Epidemiology, Biomarkers & Prevention*, 8:5 (May 1999), pp. 427-431.

61 Smith, C. J., Steichen, T. J., and Fischer, T. H. "Platelet Aggregation in Cigarette Smokers: A Meta-Analysis," *Inhalation Toxicology*, 10 (1998), pp. 765-793.

62 Ademoglu, E., Alkan, G, and Gökkusu, C. "Plasma and Erythrocyte Lipid Peroxidation in Smokers," *Biochemical Archives*, 13 (1997), pp. 269-275.

63 US Department of Health, Education, and Welfare, Public Health Service, Office of Smoking and Health. *Smoking and Health: A Report of the Surgeon General*, DHEW Publication No. (PHS) 79-50066, US Government Printing Office, 1979, Chapter 6.

64 Howard, G., Burke, G. L., Szklo, M., Tell, G. S., Eckfeldt, J., Evans, G., and Heiss, G. "Active and Passive Smoking Are Associated With Increased Carotid Wall Thickness," *Archives of Internal Medicine*, 154:11 (June 1994), pp. 1277-1282.

65 Diez-Roux, A. V., Nieto, F. J., Comstock, G. W., Howard, G., and Szklo, M. "The Relationship of Active and Passive Smoking to Carotid Atherosclerosis 12-14 Years Later," *Preventive Medicine*, 24:1 (January 1995), pp. 48-55.

66 R. J. Reynolds Tobacco Company. *Chemical and Biological Studies on New Cigarette Prototypes That Heat Instead of Burn Tobacco*, R. J. Reynolds Tobacco Company, 1988, Chapter 7.

67 Bartsch, H., Caporaso, N., Coda, M., Kadlubar, F., Malaveille, C., Skipper, P., Talaska, G., Tannenbaum, S. R., and Vineis, P. "Carcinogen Hemoglobin Adducts, Urine Mutagenicity, and Metabolic Phenotype in Active and Passive Smokers," *Journal of the National Cancer Institute*, 82:23 (December 1990), pp. 1826-1831.

68 Takagi, Y., Osada, H., Kuroishi, T., Kondo, M., Niimi, T., Saji, S., Gazdar, A. F., Takahashi, T., Minna, J. D., and Takahashi, T. "p53 Mutations in Non-Small-Cell Lung Cancers in Individuals Without a Past History of Active Smoking," *British Journal of Cancer*, 77:10 (1998), pp. 1568-1572.

69 Perera, F., Mayer, J., Jaretzki, A., Hearne, S., Brenner, D., Young, T. L., Fischman, H. K., Grimes, M., Grantham, S., Tang, M. X., Tsai, W-Y., and Santella, R. M. "Comparison of DNA Adducts and Sister Chromatid Exchange in Lung Cancer Cases and Controls," *Cancer Research*, 49:16 (August 1989), pp. 4446-4451.

70 Garner, R. C., Tierney, B., and Phillips, D. H., "A Comparison of ^{32}P-Postlabelling and Immunological Methods to Examine Human Lung DNA for Benzo[a]Pyrene Adducts," in *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention*, Bartsch, H., Hemminki, K., and O'Neill, I. K., Eds., *IARC Scientific Publications No. 89* (1988), pp. 196-201.

71 Karahalil, B., Karakaya, A. E., Burgaz, S. "The Micronucleus Assay in Exfoliated Buccal Cells: Application to Occupational Exposure to Polycyclic Aromatic Hydrocarbons," *Mutation Research*, 442:1 (June 1999), pp. 29-35.

72 Wogan, G. N. "Summary: Methods," in *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention*, Bartsch, H., Hemminki, K., and O'Neill, I. K., Eds., *IARC Scientific Publications No. 89* (1988), pp. 9-12.

73 Jarvis, M., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C., and Salloojee, Y. "Biochemical Markers of Smoke Absorption and Self Reported Exposure to Passive Smoking," *Journal of Epidemiology and Community Health*, 38:4 (December 1984), 335-339.

74 Committee on Biological Markers of the National Research Council. "Biological Markers in Environmental Health Research," *Environmental Health Perspectives*, 74 (October 1987), pp. 3-9.

75 Committee on Medical and Biological Effects of Environmental Pollutants. *Carbon Monoxide*, National Academy of Sciences, 1977, Chapters 4 and 5.

76 Hecht, S. S. "Tobacco Smoke Carcinogens and Lung Cancer," *Journal of the National Cancer Institute*, 91:14 (July 1999), pp. 1194-1210.

77 Hecht, S. S., Carmella, S. G., Chen, M., Koch, J. F. D., Miller, A. T., Murphy, S. E., Jensen, J. A., Zimmerman, C. I., and Hatsukami, D. K. "Quantification of Urinary Metabolites of a Tobacco-specific Lung Carcinogen after Smoking Cessation," *Cancer Research*, 59:3 (February 1999), 590-596.

78 Bryant, MS., Vineis, P., Skipper, P. L., and Tannenbaum, S. R. "Haemoglobin Adducts of Aromatic Amines in People Exposed to Cigarette Smoke," in *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention,* Bartsch, H., Hemminki, K., and O'Neill, I. K., Eds., *IARC Scientific Publications No. 89* (1988), pp. 133-136.

79 Bryant, MS., Vineis, P., Skipper, P. L., and Tannenbaum, S. R. "Haemoglobin Adducts of Aromatic Amines: Associations with Smoking Status and Type of Tobacco," *Proceedings of the National Academy of Sciences USA*, 85:24 (December 1988), pp. 9788-9791.

80 Vineis, P. "The Use of Biomarkers in Epidemiology: The Example of Bladder Cancer," *Toxicology Letters*, 64-65 (December 1992), pp. 463-476.

81 Dallinga, J. W., Pachen, D. M. F. A., Wijnhoven, S. W. P., Breedijk, A., van't Veer, L., Wigbout, G., van Zandwijk, N., Maas, L. M., van Agen, E., Kleinjans, J. C. S., and van Schooten, F-J. "The Use of 4-Aminobiphenyl Hemoglobin Adducts and Aromatic DNA Adducts in Lymphocytes of Smokers as Biomarkers of Exposure," *Cancer Epidemiology, Biomarkers & Prevention*, 7:7 (July 1998), pp. 571-577.

82 Yu, M. C., Ross, R. K., Chan, K. K., Henderson, B. E., Skipper, P. L., Tannenbaum, S. R., and Coetzee, G. A. "Glutathione *S*-Transferase M1 Genotype Affects Aminobiphenyl-hemoglobin Adduct Levels in White, Black, and Asian Smokers and Nonsmokers," *Cancer Epidemiology, Biomarkers & Prevention*, 4:8 (December 1995), pp. 861-864.

83 Bergmark, E. "Hemoglobin Adducts of Acrylamide and Acrylonitrile in Laboratory Workers, Smokers, and Nonsmokers," *Chemical Research Toxicology*, 10:1 (1997), pp. 78-84.

84 Perez H. L., Segerback, D., and Osterman-Golkar, S. "Adducts of Acrylonitrile with Hemoglobin in Nonsmokers and in Participants in a Smoking Cessation Program," *Chemical Research Toxicology*, 12:10 (October 1999), pp. 869-873.

85 Wallace, L. A., Pellizzari, E., Hartwell, T. D., Perritt, R., and Ziegenfus, R. "Exposure to Benzene and Other Volatile Compounds from Active and Passive Smoking," *Archives of Environmental Health*, 42:5 (September-October 1987), pp. 272-279.

86 Scherer, G., Ruppert, T., Daube, H., Kossien, I., Riedel, K., Tricker, A. R., and Adlkofer, F. "Contribution of Tobacco Smoke to Environmental Benzene Exposure in Germany," *Environmental International*, 21:6 (1995), pp. 779-789.

87 Ghittori, S., Imbriani, M., Maestri, L., Capodaglio, E., Cavalleri, A. "Determination of S-Phenylmercapturic Acid in Urine as an Indicator of Exposure to Benzene," *Toxicology Letters*, 108:2-3 (September 1999), pp. 329-334.

88 Melikian, A. A., Sun, P., Pierpoint, C., Coleman, S., and Hecht, S. S. "Gas Chromatographic-Mass Spectrometric Determination of Benzo[a]pyrene and Chrysene Diol Epoxide Globin Adducts in Humans," *Cancer Epidemiology, Biomarkers & Prevention*, 6:10 (October 1997), pp. 833-839.

89 Crawford, F. G., Mayer, J., Santella, R. M., Cooper, T. B., Ottman, R., Tsai, W. Y., Simon-Cereijido, G, Wang, M., Tang, D., and Perera, F. P. "Biomarkers of Environmental Tobacco Smoke in Preschool Children and Their Mothers," *Journal of the National Cancer Institute*, 86:18 (September 1994), pp. 1398-1402.

90 Davis, J. W., Shelton, L., Watanabe, I. S., and Arnold, J. "Passive Smoking Affects Endothelium and Platelets," *Archives of Internal Medicine*, 149:2 (February 1989), pp. 386-389.

91 Iso, H., Shimamoto, T., Sato, S., Koike, K., Iida, M., and Komachi, Y. "Passive Smoking and Plasma Fibrinogen Concentrations," *American Journal of Epidemiology*, 144:12 (December 1996), pp. 1151-1154.

92 Feldman, J., Shenker, I. R., Etzel, R. A., Spierto, F. W., Lilienfield, D. E., Nussbaum, M., Jacobson, M. S. "Passive Smoking Alters Lipid Profiles in Adolescents," *Pediatrics*, 88:2 (August 1991), pp. 259-264.

93 Moskowitz, W. B., Mosteller, M., Schieken, R. M., Bossano, R., Hewitt, J. K., Bodurtha, J. N., and Segrest, J. P. "Lipoprotein and Oxygen Transport Alterations in Passive Smoking Preadolescent Children. The MCV Twin Study," *Circulation*, 81:2 (February 1990), pp. 586-592.

94 Coggins, C. R. E. "A Review of Chronic Inhalation Studies with Mainstream Cigarette Smoke in Rats and Mice," *Toxicologic Pathology*, 26:3 (May-June 1998), pp. 307-314.

95 Gori, G. B., Ed. *Report No. 5. Toward Less Hazardous Cigarettes. Summary: Four Skin Painting Bioassays Using Condensate from Experimental Cigarettes*, U.S. Department of Health, Education, and Welfare, US Government Printing Office, 1980.

96 Steele, R. H., Payne, V. M., Fulp, C. W., Rees, D. C., Lee, C. K., and Doolittle, D. J. "A Comparison of the Mutagenicity of Mainstream Cigarette Smoke Condensates from a Representative Sample of the U.S. Cigarette Market with a Kentucky Reference Cigarette (K1R4F)," *Mutation Research*, 342:3-4 (April 1995), pp. 179-190.

97 Kier, L. D., Yamasaki, E., and Ames, B. N. "Detection of Mutagenic Activity in Cigarette Smoke Condensates," *Proceedings of the National Academy of Sciences*, 71:10 (October 1974), pp. 4159-4163.

98 US Department of Health and Human Services, Office of Smoking and Health. *The Health Consequences of Smoking-The Changing Cigarette: A Report of the Surgeon General*, DHHS Publication No. (PHS) 81-50156, US Government Printing Office, 1981, p. 43.

99 Mauderly, J. L., Bechtold, W. E., Bond, J. A., Brooks, A. L., Chen, B. T., Cuddihy, R. G., Harkema, J. R., Henderson, R. F., Johnson, N. F., Rithidech, K, and Thomassen, D. G. "Comparison of 3 Methods of Exposing Rats to Cigarette Smoke," *Experimental Pathology*, 37 (1989), pp. 194-197.

100 US Department of Health and Human Services, Office of Smoking and Health. *The Health Consequences of Smoking-Cancer: A Report of the Surgeon General*, DHHS Publication No. (PHS) 82-50179, US Government Printing Office, 1982, p. 218.

101 Sorrentino, C., del Piano, L., Abet, M., and Di Muro, A. "Indagine Preliminare Sulla Mutagenicità del Condensato nei Principali Tipi Tabacco Italiano," *Il Tabacco*, 4 (1996), pp. 47-50.

102 Coggins, C. R. E., Fouillet, X. L. M., Lam, R., and Morgan, K. T. "Cigarette Smoke Induced Pathology of the Rat Respiratory Tract: A Comparison of the Effects of the Particulate and Vapour Phases," *Toxicology*, 16 (1980), pp. 83-101.

103 Bombick, B. R., Murli, H., Avalos, J. T., Bombick, D. W., Morgan, W. T., Putnam, K. P., and Doolittle, D. J. "Chemical and Biological Studies of a New Cigarette that Primarily Heats Tobacco. Part 2. *In Vitro* Toxicology of Mainstream Smoke Condensate," *Food and Chemical Toxicology*, 36:3 (March 1998), pp. 183-190.

104 Bombick, D. W., Ayres, P. H., Putnam, K. P., Bombick, B. R., and Doolittle, D. J. "Chemical and Biological Studies of a New Cigarette that Primarily Heats Tobacco. Part 3. *In Vitro* Toxicology of Whole Smoke," *Food and Chemical Toxicology*, 36:3 (March 1998), pp. 191-197.

105 Clapp, W. L., Fagg, B. S., and Smith, C. J. "Reduction in Ames *Salmonella* Mutagenicity of Mainstream Cigarette Smoke Condensate by Tobacco Protein Removal," *Mutation Research*, 446:2 (December 1999), pp. 167-174.

106 Chortyk, O. T. and Chamberlain, W. J. "A Study on the Mutagenicity of Tobacco Smoke from Low-"Tar" Cigarettes," *Archives of Environmental Health*, 45:4 (July/August 1990), pp. 237-244.

107 Green, C. R. and Rodgman, A. "The Tobacco Chemists' Research Conference: A Half Century Forum for Advances in Analytical Methodology of Tobacco and Its Products," *Recent Advances in Tobacco Science*, 22 (October 1996), pp. 131-304.

108 U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress-A Report of the Surgeon General*, DHHS Publication No. (CDC) 89-8411, US Government Printing Office, 1989, pp. 79-88.

109 Hoffman, D. "Analysis of Toxic Smoke Constituents," A report prepared for the U. S. Consumer Product Safety Commission under contract CPSC-S-92-5473, March 1993.

110 National Cancer Institute Smoking and Tobacco Control Program. *The FTC Cigarette Test Method for Determining "Tar", Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes: Report of the NCI Expert Committee*, U.S. National Institutes of Health, 1996; monograph 7 in the Smoking and Tobacco Control series, Chapters 1-3.

111 Hoffmann, D., Rivenson, A., Murphy, S. E., Chung, F-L., Amin, S., and Hecht, S. S. "Cigarette Smoking and Adenocarcinoma of the Lung: The Relevance of Nicotine-Derived *N*-Nitrosamines," *Journal of Smoking-Related Disorders*, 4:3 (1993), pp. 165-189.

112 Tricker, A. R. and Preussmann, R. "Volatile *N*-Nitrosamines in Mainstream Cigarette Smoke: Occurrence and Formation," *The Clinical Investigator*, 70 (1992), pp. 283-298.

113 Gori, G. B., Ed. *Report No. 4. Toward Less Hazardous Cigarettes. The Fourth Set of Experimental Cigarettes*, U.S. Department of Health, Education, and Welfare , US Government Printing Office, 1980.

114 Dumont, J., Larocque-Lazure, F., and Iorio, C. "An Alternative Isolation Procedure for the Subsequent Determination of Benzo[a]Pyrene in Total Particulate Matter of Cigarette Smoke," *Journal of Chromatographic Science*, 31:9 (September 1993), pp. 371-374.

115 Manning, D. L., Maskarinec, M. P., Jenkins, R. A., and Marshall, A. H., "High Performance Liquid Chromatographic Determination of Selected Gas Phase Carbonyls in Tobacco Smoke," *Journal of the Association of Official Analytical Chemists*, 66:1 (1983), pp. 8-12.

116 Brunnemann, K. D., Kagan, M. R., Cox, J. E., and Hoffmann, D. "Analysis of 1,3-Butadiene and Other Selected Gas-phase Components in Cigarette Mainstream and Sidestream Smoke by Gas Chromatography-Mass Selective Detection," *Carcinogenesis*, 11:10 (October 1990), pp. 1863-1868.

117 DeBardeleben, M. Z., Wickham, J. E ., and Kuhn, W. F. "The Determination of "Tar" and Nicotine from an Historical Perspective," *Recent Advances in Tobacco Science*, 17 (1991), pp. 115-148.

118 Schmeltz, I. and Hoffmann, D. "Nitrogen-Containing Compounds in Tobacco and Tobacco Smoke," *Chemical Reviews*, 77:3 (June 1977), pp. 295-311.

119 Church, D. F. and Pryor, W. A. "Free-Radical Chemistry of Cigarette Smoke and Its Toxicological Implications," *Environmental Health Perspectives*, 64 (1985), pp. 111-126.

120 Eiserich, J. P., Vossen, V., O'Neill, C. A., Halliwell, B., Cross, C. E., and van der Vliet, A. "Molecular Mechanisms of Damage by Excess Nitrogen Oxides: Nitration of Tyrosine by Gas-phase Cigarette Smoke," *FEBS Letters*, 353 (1994), pp. 53-56.

121 Brunnemann, K. D., Yu, L., and Hoffmann, D. "Chemical Studies on Tobacco Smoke. XLIX. Gas Chromatographic Determination of Hydrogen Cyanide and Cyanogen in Tobacco Smoke," *Journal of Analytical Toxicology*, 1 (January/February 1977), pp. 38-42.

122 Klus, H. "Distribution of Mainstream and Sidestream Cigarette Smoke Components," *Recent Advances in Tobacco Science*, 16 (1990), pp. 189-232.

123 Hecht, S. S., Carmella, S., Mori, H., and Hoffmann, D. "A Study of Tobacco Carcinogenesis. XX. Role of Catechol as a Major Cocarcinogen in the Weakly Acidic Fraction of Smoke Condensate," *Journal of the National Cancer Institute*, 66:1 (January 1981), pp. 163-169.

124 Tomkins, B. A., Jenkins, R. A., Griest, W. H., Reagan, R. R., and Holladay, S. K., "Liquid Chromatographic Determination of Phenol and Cresols in Total Particulate Matter of Cigarette Smoke," *Journal of the Association of Official Analytical Chemists*, 67:5 (1984), pp. 919-923.

125 Brunnemann, K. D., Kagan, M. R., Cox, J. E., and Hoffmann, D. "Determination of Benzene, Toluene, and 1,3-Butadiene in Cigarette Smoke by GC-MSD," *Experimental Pathology*, 37 (1989), pp. 108-113.

126 Nitsch, A. and Kalcher, K. "Schwermetalle in Tabaken und in Tabakrausch II. Spurenelemente Cadmium, Blei, Kupfer, Kobalt und Nickel in österreichischen Zigaretten und deren Rauchkondensaten und Rauchgasen," *Beiträge zur Tabakforschung International*, 15 (August 1991), pp. 19-32.

127 Krivan, B., Schneider, G., Baumann, H., and Reus, U. "Multi-element Characterization of Tobacco Smoke Condensate," *Fresenius Journal of Analytical Chemistry*, 348 (1994), pp. 218-225.

128 Rhoades, C. B., Jr. and White, R. T., Jr. "Mainstream Smoke Collection by Electrostatic Precipitation for Acid Dissolution in a Microwave Digestion System Prior to Trace metal Determination," *Journal of AOAC International*, 80 (1997), pp. 1320-1331.

129 Halliwell, B. and Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*, Claridon Press, 1985, Chapter 6.

130 Hwang, D., Chanmugam, P., Boudreau, M., Sohn, K. H., Stone, K., and Pryor, W. A. "Activation and Inactivation of Cyclo-Oxygenase in Rat Alveolar Macrophages by Aqueous Cigarette Tar Extracts," *Free Radical Biology & Medicine*, 27:5/6 (1999), pp. 673-682.

131 El-Bayoumy, K., O'Donnell, M., Hecht, S. S., and Hoffmann, D. "On the Analysis of 1-Nitronaphthalene, 1-Nitropyrene and 6-Nitrochrysene in Cigarette Smoke," *Carcinogenesis*, 6:4 (1985), pp. 505-507.

132 Totsuka, Y., Ushiyama, H., Ishihara, J., Sinha, R., Goto, S., Sugimura, T., and Wakabayashi, K. "Quantification of the Co-mutagenic β-Carbolines, Norharman, and Harman, in Cigarette Smoke Condensates and Cooked Foods," *Cancer Letters*, 143 (1999), pp. 139-143.

133 Gori, G. B., Ed. *Report No. 2. Toward Less Hazardous Cigarettes. The Second Set of Experimental Cigarettes*, DHEW Publication No. (NIH) 76-1111, US Government Printing Office, 1976.

134 Sakuma, H., Kusama, M., Munakata, S., Ohsumi, T., and Sugawara, S. "The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. Part I. Acidic Components," *Beiträge zur Tabakforschung International*, 12:1 (June 1983), pp. 63-71.

135 Sakuma, H., Kusama, M., Yamaguchi, K., Matsuki, T., and Sugawara, S. "The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. Part II. Bases," *Beiträge zur Tabakforschung International*, 12:4 (July 1984), pp. 199-209.

136 Sakuma, H., Kusama, M., Yamaguchi, K., and Sugawara, S. "The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. Part III. Middle and Higher Boiling Components," *Beiträge zur Tabakforschung International*, 12:5 (November 1984), pp. 251-258.

137 Norman, V. "The Effect of Perforated Tipping Paper on the Yield of Various Smoke Components," *Beiträge zur Tabakforschung*, 7 (September 1974), 282-287.

138 Hoffmann, D., Djordjevic, M. V., and Brunnemann, K. D. "Changes in Cigarette Design and Composition Over Time and How They Influence the Yields of Smoke Constituents," *Journal of Smoking-Related Disorders*, 6:9 (1995), pp. 9-23.

139 Vickroy, D. G. "The Characterization of Cigarette Smoke from Cytrel® Smoking Products and Its Comparison to Smoke from Flue-Cured Tobacco. I. Vapor Phase Analysis," *Beiträge zur Tabakforschung*, 8:7 (October 1976), 415-421.

140 Mauldin, R. K. "The Characterization of Cigarette Smoke from Cytrel® Smoking Products and Its Comparison to Smoke from Flue-Cured Tobacco. II. Semi-Volatile Phase Analysis," *Beiträge zur Tabakforschung*, 8:7 (October 1976), 422-429.

141 Allen, R. E. and Vickroy, D. G. "The Characterization of Cigarette Smoke from Cytrel® Smoking Products and Its Comparison to Smoke from Flue-Cured Tobacco. III. Particulate Phase Analysis," *Beiträge zur Tabakforschung*, 8:7 (October 1976), 430-437.

142 R. J. Reynolds Tobacco Company. *Chemical and Biological Studies on New Cigarette Prototypes That Heat Instead of Burn Tobacco*, R. J. Reynolds Tobacco Company, 1988, Chapters 3 and 4.

143 Borgerding, M. F., Bodnar, J. A., Chung, H. L., Mangan, P. P., Morrison, C. R., Risner, C. H., Rogers, J. C., Simmons, D. F., Uhrig, M. S., Wendelboe, F. N., Wingate, D. E., and Winkler, L. S. "Chemical and Biological Studies of a New Cigarette that Primarily Heats Tobacco. Part 1. Chemical Composition of Mainstream Smoke," *Food and Chemical Toxicology*, 36:3 (March 1998), pp. 169-182.

144 DeBardeleben, M. Z., Clafin, W. L., and Gannon, W. F. "Role of Cigarette Physical Characteristics on Smoke Composition," *Recent Advances in Tobacco Science*, 4 (1978), pp. 85-111.

145 Chortyk, O. T. and Schlotzhauer, W. S., "The Contribution of Low "Tar" Cigarettes to Environmental Tobacco Smoke," *Journal of Analytical Toxicology*, 13 (May/June 1989), pp. 129-134.

146 Massachusetts Department of Public Health. "1997 Cigarette Nicotine Disclosure Report as Required by Massachusetts General Laws, Chapter 307B, CMR 660.000," Massachusetts Department of Public Health, Boston, MA, January 16, 1998.